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(54) Title: USE OF ANTIVIRAL COATING FOR LATEX ITEMS SUCH AS CONDOMS

(57) Abstract

An antiviral cream or lotion for application to mammalian skin, under a protective skin barrier such as a surgical glove or condom, comprises a very small skin-tolerable amount of an alkyl benzyl quaternary ammonium halide disinfectant, a very small, skin-tolerable amount of a nonionic or cationic surfactant, a thickener such as aquasonic gel, an emollient such as glycerine, and water.

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USE OF ANTIVIRAL COATING FOR LATEX ITEMS SUCH AS CONDOMS.

FIELD OF THE INVENTION

This invention relates to anti-viral compositions, and more particularly to anti-viral compositions for external topical application to mammalian skin.

BACKGROUND OF THE INVENTION AND PRIOR ART

Viral transmission from body to body as a result of body surface contact and body fluid intermingling is one of the principal ways in which viruses such as hepatitis, herpes, HIV and the like are spread. Particularly at risk from such viral transmissions are health workers such as ambulance personnel, nurses, doctors, operations theatre attendants and the like, who must administer to and consequently frequently engage in body contact with virally infected persons. To date, the most commonly recommended form of protection against such viral infections has been the protective skin barrier method namely the use of latex gloves by health care workers and the use of latex condoms by those exposed to sexually transmitted viruses.

There is still a degree of concern, however, about the effectiveness of such skin barrier items. The items must be extremely thin if they are to permit the use of the required degree of sensitivity during their use. The thinner such latex items become, the greater the risk of physical damage to them, and the greater the risk of their proving permeable, to a greater or lesser extent to the virus particles they are intended to contain. Moreover, however carefully such barrier items are manufactured and stored, there is always a risk that areas of them will have excess porosity.

It is an object of the present invention to enhance the efficiency of such latex skin barrier items in preventing the transmission of harmful viruses from body to body.

SUMMARY OF THE INVENTION

The present invention provides an anti-viral gel formulation for use in conjunction with viral barrier items such as latex gloves and condoms. The formulation contains a very small, skin acceptable amount of a strong disinfectant or antiseptic substance, formulated into a semi-solid, gel consistency with aqueous based, skin acceptable carrier materials, for application to mammalian skin under viral barrier items such as latex gloves and condoms. The disinfectant or antiseptic substance kills the harmful virus on contact, even in the necessarily small concentrations required to render the compositions of the present invention skin acceptable. The user is accordingly provided with a double protection against viral infection from an infected body which must be contacted, namely the viral barrier item and the antiseptic or disinfectant gel beneath it.

Thus, according to the present invention, from one aspect, there is provided a latex barrier item adapted to be fitted over a body part to inhibit viral transmission thereto, said latex barrier item having an outer surface and an inner surface to contact the body part, said inner surface having a layer of semi-solid, anti-viral gel or cream comprising an alkyl benzyl quaternary ammonium halide disinfectant in an amount of from about 0.005-0.1% by weight, a non-ionic or cationic surfactant in an amount of from about 0.01-0.1% by weight, and a lubricious non-toxic hypoallergenic water compatible thickener in an amount chosen to give semi-solid, creamy consistency to the composition, and water.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The alkyl benzyl quaternary ammonium halide disinfectants used in the present invention are known compounds, many of which have previously been sold and used for disinfecting purposes in non-skin contacting applications. Thus, they are sold for purposes of making up disinfectant wash solutions for floors, walls, operating surfaces and the like, but always with strong warnings to avoid skin contact with them if at all possible. They are powerful poisons and skin irritants, as well as powerful disinfectants. According to the present invention, they will destroy harmful viruses such as hepatitis, herpes simplex types 1 and 2 and HIV when they are present in formulations in such low concentrations that they are skin acceptable. These viruses in fact are not difficult to kill when encountered in isolation in external body fluids or secretions. It is after they have infected the mammalian body and begun to replicate in the body cells that they become almost impossible to treat effectively. If the viruses can be caught and treated on transmission from body to body, they are vulnerable to common disinfectants such as those used in the compositions of the present invention.

To safeguard against risks of skin irritation, the strong disinfectant is preferably used in the composition of the present invention in amounts from 0.005-0.5% by weight, most preferably from 0.005-0.001% by weight. Specific examples of such strong disinfectants for use in the present invention include alkyl dimethyl benzyl ammonium chloride and alkyl dimethylethylbenzyl ammonium chloride, in which the alkyl portions are C_{12}-C_{18} in length, and mixtures thereof, and myristylbenzalkonium chloride. Such a suitable mixture is available commercially under the trade name MAQUAT MQ2525M - 50%, from Mason Chemical Company, Chicago, Illinois, and under the trade name BTC 2125M from Stepan Company, North Field, Illinois.

Compositions according to the present invention also include a small amount of a non-ionic or cationic surfactant to act as a wetting agent for the disinfectant. This improves the spreading of the disinfectant over the skin area to which it is applied. The surfactant is suitably present in amounts similar to those of the disinfectant, i.e. 0.01-0.1% by weight, preferably 0.01-0.05% by weight. Examples of specific useful surfactants of these classes include the polyoxyethylene - based types such as those of the octoxynol series , which are polyethylene glycol p-isooctylphenyl ethers such as octoxynol-9 (Triton X - 100), those of the nonoxynol series, which are polyoxyethylene nonylphenyl ethers, of various numbers of ethylene oxide units, e.g. nonoxydol 9 and nonoxydol 10. These have the advantage for use in the present invention in that they also have spermatocidal properties. Another type of suitable polyoxyethylene based non-ionic surfactants are the polyoxyethyl alcohols such as those sold under the trade name "Siponic." Other choices of surfactant may be made by consulting the standard reference work: "Non-Ionic Surfactants," edited by M.J.Schick, Dekker, New York, 1967. The overriding criteria of choice are compatibility with skin and with the chosen strong disinfectant, at the chosen amounts.

The other ingredients of the composition of the present invention are a non-toxic hypoallergenic water compatible thickener, and water, in proportions suitable to provide a product of a gel, semi-solid consistency resembling that of hand cream. A wide range of such thickeners is available on the market, and commonly used in the cosmetic and pharmaceutical formulations industries. They are well known to those skilled in the art. Various cellulose derivatives can be used for this purpose, for example methyl cellulose and the various sodium carboxymethyl cellulose compounds such as Carbomers 910, 934, 934P, 940, 941 and 1342; and Carbopols 940, 941 and 930 (from

Goodyear). Preferred are those which also confer a degree of lubricity on the final composition. Especially preferred is aquasonic gel, a gel composition commonly used for body contact with ultra sound diagnostic test apparatus. It suitably comprises from 1 - 80%, preferably from 20 - 80% and most preferably from 30-40% by weight of the composition. The amount is chosen on the basis of the desired consistency of the final product, and on the basis of the precise choice of thickener - some have greater thickening power than others.

Various additional ingredients can be added to the composition of the present invention to improve the nature and encourage the use thereof. Thus, it can contain one or more emollients such as glycerine, lanolin, aloe vera, paraffin oils, glycerol monostearate, myrj compounds, Tween, PEG compounds, sodium lauryl sulphate, etc., and mixtures of two or more of them, to improve the lubricity and general oiliness of the composition. It can also if desired contain various perfumes and colorants. Any ingredients which are used must be skin compatible, inert towards the active ingredient, and of a nature and used in an amount which does not destabilize or upset the general creamy consistency of the formulation.

The formulations according to the present invention can be prepared using standard cosmetic or pharmaceutical gel formulating procedures and equipment. There is no particular, critical order of addition of components, mixing temperatures or the like, provided that a homogeneous, reasonably stable end product is achieved.

SPECIFIC DESCRIPTION OF THE MOST PREFERRED EMBODIMENT

The specific, most preferred formulation according to the present invention has the following composition (parts by weight):

Water	53.74
Aquasonic gel	42.50
Glycerin	2.27
Aloe Vera Oil	1.19
Triton X-100	0.10 (octoxynol-9)
MQ 2525-50%	0.05
Fragrance (vanilla extract)	0.15

The invention is further described and illustrated in the following specific, non limiting examples.

EXAMPLE 1

An emulsion formulation according to the invention of semi-solid, cream-like consistency, was made up from the following components (percent by weight):

EDTA Tetrasodium salt	0.05
Octoxynol-9 (Triton X-100)	0.02
BTC-2125	0.05
Glycerin	0.05
Methyl Cellulose (4000 cps)	1.0
Siponic C-20	5.0
Water	93.83

The preparation was made by simple mixing of ingredients in a container, at room temperature. It was then tested for its anti-viral effectiveness in vitro against Herpes Hominis types 1 and 2.

Clinical isolates where obtained of Herpes Hominis type 1 and 2, specifically:

Type 1 isolates 103, 104, 105, 117
Type 2 isolates 109, 106,142

Virus suspensions were clarified by low speed centrifugation and kept frozen at -70°C. Infectivity was titrated and expressed in TCID 50/0.1 ml.

Equal volumes of virus were added to the test formulation in the concentration given in the following table of results. Thus, the most concentrated emulsion was 10% after the virus was added.

The inoculated mixtures were incubated at 22°C for 10 minutes. 10 fold dilutions were then quickly made with chilled medium. Residual infectivity was then determined by using 4 tubes of cell culture per tube dilution. The results are expressed as TCID 50/0.1 ml. Controls were used consisting of medium without the test formulation.

TABLE OF RESULTS:

	INFECTIVITY ($TCID_{50}$) AFTER TEST FORMULATION CONTACT								
ISOLATE	10%	5%	2.5%	1%	.5%	.05%	.005%	.0005%	CONTROL
H. HOMINIS, TYPE 2									
109	<1	<1	<1	<1	<1	<1	<1	2.0	3.0
116	<1	<1	<1	<1	<1	<1	<1	3.0	3.0
142	<1	<1	<1	<1	<1	<1	<1	2.0	3.0
H. HOMINIS TYPE 1									
103	<1	<1	<1	<1	<1	<1	3.0	3.0	3.0
104	<1	<1	<1	<1	<1	<1	3.0	3.0	3.0
105	<1	<1	<1	<1	<1	<1	<1	2.0	3.0
117	<1	<1	<1	<1	<1	<1	<1	3.0	3.0

After incubation the residual test formulation activity had been reduced to an undetectable level in all the test formulations/virus mixtures at concentrations of 10, 5, 2.5, 1, 0.5, 0.05% of test formulation. The controls consisting of medium contained 3.0 and 4.0 log ten TCID 50/0.1 ml. The reductions in the titers of virus after contacting with 10, 5, 2.5, 1, 0.5, 0.05% test formulation were in excess of 2 log 10 $TCID_{50}$.

In order to confirm the experiments, the test formulation/virus mixtures were incubated at 37°C for 10 minutes and the same inactivity resulted with both types of herpes virus.

EXAMPLE 2 - TOXICITY STUDY

A cream was formulated having the same ingredients in the same relative proportions as described above in Example 1.

10 rats were shaved to expose posterior epidermis. The cream was then applied topically to each rat in the exposed area and observed 48 hours. The results are given below:

RESULTS:

RAT #	# APPLICATIONS	TOXICITY
1	1	-
2	1	-
3	1	-
4	1	-
5	1	-
6	4*	-
7	4	-
8	4	-
9	4	-
10	4	-

- Indicates no visual sign of toxicity present in 48 hr. period.

* Cream applied at 4 hour intervals for a total of 4 applications.

EXAMPLE 3

A cream formulation according to the specific, most preferred formulation given above was tested for its effectiveness against human hepatitis B in the morphological alteration test and destruction test.

A human hepatitis B virus (HBV) formulation was prepared having 5.0% bovine calf serum (40 µl) with 760 µl HBV (Gilbralter Biological Laboratories, Inc., HBV Pool 11, GBL reference no. 018-272A-153). Into 25 x 150 mm glass tubes was injected 2 ml of the cream formulation and 0.2 ml of the HBV formulation. The mixtures were vortexed vigorously for one minute. The reaction was stopped by adding 18 ml of Trypticase Soy Broth containing 20% serum, vortexing well and placing into ice bath. Virus controls were prepared in the same way by pipetting 0.2 ml HBV into 2.0 ml phosphate buffered saline (PBS). The reaction mixtures were concentrated by ultracentrifugation with appropriate sucrose gradients, the supernatant gently poured off, and the pellets were re-suspended with a 0.5 ml PBS, with similar pellets being combined. The HBV particles were purified by late-zonal ultracentrifugation in a 60-5% linear gradient (sucrose), and fractionated. Dane particle fractions having a refractive index between 1.396 and 1.404 were saved and pooled.

Positive staining was used to quantitate the number of virions destroyed by the test formulation. This was done with potassium permanganate (2%) and blotting, followed by deionized water and blotting, followed by

uranyl acetate (1.5%) and blotting. Ten fields from 20 randomly selected squares were observed with a Philips transmission electron microscope, and counted at 50,000 magnification. No virions were detected. By comparison with the controls, it was evident that greater than 40,000 virions had been destroyed in one minute.

Negative staining was used to detect morphologically altered virions. For this, 5% uranyl acetate in water, at pH 3.5, was used, with blotting. Thirty or more fields from six randomly selected squares were observed with a Philips transmission electron microscope, and thoroughly enumerated for each of the four alteration phases AP0, AP1, AP2 and AP3. No morphologically intact virions were observed, only highly morphologically altered, AP2 and AP3 forms, which are non-infectious. In contrast, the control samples evidenced the great majority of virions to be morphologically intact and in the infectious (AP0 or AP1) phases.

The mechanism of action of the composition of the invention is probably membrane disruption.

EXAMPLE 4

The cream according to the specific, most prepared formulation according to the invention, was tested for *in vitro* inactivation of HIV.

The human T-cell leukemia virus type 1 immortalized cell line MT-2 was maintained in growth medium (Dulbecco's Modified Eagle's Medium with 15% heat-inactivated fetal calf serum, 2 mm glutamine, 100 iu of penicillin per ml and 100 μg of streptomycin per ml).

HIV-1 (IIIB) the prototype laboratory strain, was obtained from the culture supernatant of H9 infected cells

and was concentrated to 1,000 x by banding in sucrose. Filtered viral stocks were aliquoted and stored at -85°C until used. The virus stock was determined by an end point titration method using MT-2 cells in a 96-well microtiter plate configuration. The virus stock contained a TCID 50 virus titer of 5.50 log 10 TCID 50/ml calculated by the Reed-Muench method.

In order to perform cytotoxicity studies, MT-2 cells in exprudential growth phase were exposed to various dilutions of compounds. After 4 days, the cell viability was assessed by the Tryptan-Glu exclusion method and compared to controls without drug.

Virus stocks were thawed and diluted with phosphate buffered saline to obtain the required amounts of virus necessary for inactivation assay experiments. Untreated virus served as the TCID 50 control for this experiment. After a one minute exposure of HIV-1 with the compound, sequential ten-fold dilutions of the treated or untreated virus control were prepared in PBS and each dilution was used to infect MT-2 cells as previously described. Virus expression was monitored by the presence of syncytium formation. HIV-induced syncytium formation was assessed after 6 days of culture using a syncytium-formation assay.

The compound according to the invention yielded a reduction in HIV infectivity of greater than 2.5 log 10 TCID 50/ml, when compared with untreated controls after one minute of exposure at room temperature (23 - 27°C).

EXAMPLE 5

The effectiveness of the cream according to the specific, most preferred formulation of the invention was assessed in association with commercially available surgi-

cal latex gloves.

An operators hands were covered with cream according to the formulation described above, applying approximately 2½ cc's to each hand, and then latex surgical gloves were applied over the hands. In one case, the latex gloves contained a residue of starch lubricant powder, in conventional form. In another case, the glove contained no powder. The gloves were left in place on the users hands for 16 hours.

Then the gloves were removed, and centrifuged to draw the liquid/semi-solid contents (residual cream, users perspiration, powder sediment etc.) into one figure of the glove. Aliquots of this liquid residue were extracted, and subjected to the in vitro inactivation of HIV by the serial dilution technique against the HIV prototype laboratory strain with virus titers using MT-2 cells and ten-fold serial dilutions as described with Example 4.

The residues from the latex gloves without powder and from the latex gloves with powder sediment both showed a log virus titer reduction of greater than 3.0, as did the cream which had been subjected to the latex glove test, thereby demonstrating that the composition according to the invention maintains its HIV inactivation properties when mixed with latex gloves for at least 16 hours.

I CLAIM:

1. A latex barrier item adapted to be fitted over a body part to inhibit viral transmission thereto, said latex barrier item having an outer surface and an inner surface to contact the body part, said inner surface having a layer of semi-solid anti-viral gel or cream comprising an alkyl benzyl quaternary ammonium halide disinfectant in an amount of from about 0.005-0.1% by weight;

a non-ionic or cationic surfactant in an amount of from about 0.01-0.1% by weight;

a non-toxic hypoallergenic water compatible thickener in an amount of from about 1-80% by weight;

and water.

2. The latex barrier item of claim 1 which is a latex surgical glove or a latex condom.

3. The latex barrier item of claim 2 wherein the disinfectant is present in an amount of from about 0.005-0.05% by weight.

4. The latex barrier item of claim 3 wherein the disinfectant is present in an amount of from about 0.005 - 0.01% by weight.

5. The latex barrier item of claim 3 wherein the disinfectant is selected from the group consisting of alkyl dimethyl benzyl ammonium chloride in which the alkyl groups are from C_{12} - C_{18};

alkyl dimethyl ethylbenzyl ammonium chloride in which the alkyl groups are from C_{12} - C_{18};

and mixtures thereof.

6. The latex barrier item of claim 4 wherein the surfactant is present in an amount of from about 0.01 - 0.05%.

7. The latex barrier item of claim 6 wherein the surfactant a non-ionic surfactant of the polyoxyethylene-based type.

8. The latex barrier item of claim 7 wherein the surfactant is oxtoxynol-9.

9. The latex barrier item of claim 3 wherein the thickener is aquasonic gel.

10. The latex barrier item of claim 9 wherein the aquasonic gel is present in an amount of from about 30-40% by weight.

11. The latex barrier item of claim 3 wherein the antiviral gel or cream additionally includes an emollient.

12. The latex barrier item of claim 11 wherein the emollient is glycerine.

13. A semi-solid anti-viral gel or cream composition, for topical application to mammalian skin under a viral barrier item, said composition comprising an alkyl benzyl quaternary ammonium halide disinfectant in an amount of from about 0.005-0.1% by weight;

a non-ionic or cationic surfactant in an amount of from about 0.01-0.1% by weight;

a non-toxic hypoallergenic water compatible thickener in an amount of from about 1-80% by weight;

and water.

14. The composition of claim 13 wherein the disinfectant is selected from the group consisting of alkyl dimethyl benzyl ammonium chloride in which the alkyl groups are from C_{12}-C_{18};

alkyl dimethyl ethylbenzyl ammonium chloride in the alkyl groups are from C_{12}-C_{18};

and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 93/00115

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00; A61K7/48; A61L31/00; A61F6/04
A61K31/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K ; A61L ; A61F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X Y	EP,A,0 427 997 (GERMO) 22 May 1991 see page 2, line 51 - line 54; claims 1,2	1-5 7,8,11, 12
X	DATABASE WPIL Section Ch, Week 8316, Derwent Publications Ltd., London, GB; Class A96, AN 83-37482K & JP,A,57 209 050 (JEX) see abstract	1-5,11, 12
X	FR,A,2 623 087 (MEDIC) 19 May 1989 see page 1, line 22 - line 29; claims 1-4	1,2

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 JULY 1993	26. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	PELTRE CHR.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0 475 664 (DOW CORNING) 18 March 1992 see column 2, line 17 - line 21 see column 3, line 19 - line 23	7,8
X	L. VIDAL 'DICTIONNAIRE VIDAL' 1991 , EDITIONS DU VIDAL , PARIS, FR	13
Y	GEL LUBRIFIANT PHARMATEX see page 189	11,12
P,X	WO,A,9 209 256 (MEDICAL POLYMERS) 11 June 1992 see claims 1,3,4,8	13,14

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9300115
SA 72861

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0427997	22-05-91	None		
FR-A-2623087	19-05-89	None		
EP-A-0475664	18-03-92	FR-A-	2666587	13-03-92
		CA-A-	2050358	11-03-92
		CN-A-	1059845	01-04-92
		JP-A-	4288018	13-10-92
WO-A-9209256	11-06-92	None		